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Editorial

Exceptional cancer responders: A zone-to-go

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Cancer is a disease that implies several different genotypic and phenotypic traits in its whole process of development: tumorigenesis. Many cancers are successfully treated nowadays with the help of a multidisciplinary team. In a global patient-treatment approach, a clinical oncologist and/or a surgeon may act first, then a radiotherapist and, when clinical conditions deteriorate, a palliative care team is a must. The clinical oncologist has to be not only skillful in clinics, but also able to tackle basic research and translational medicine methods and actualizations. This allows her or him to have a grip on genomics, proteomics, metabolomics and precision medicine, which is the last very useful tool nowadays in many medical areas, including oncology [1].

Oncologists used to be very frustrated when some cancer relapses, mainly those named difficult-to-treat. This relapse is due in general to an innate tumor treatment resistance capacity that is called tumor refractoriness. In this case, the patient is medically treated at first but the disease goes on without stopping in its growth: no tumor response with first, second lines and so on. On the other hand, relapsed tumors also use to present acquired resistance that is due to awesome and complex molecular-cellular-kinetic and dynamic processes developed in response to applied treatments.

Many years ago, Braverman wrote in Annals of Internal Medicine [2] an extraordinary comment (for those days) about tumor development from the evolutionary point of view and referred to "tumor resistance or insensitivity" to chemotherapy. In this work, he proposed that all chemo-sensitive tumors are those composed of cells embryologically derived from the primitive yolk sac: gamete or blood cell precursors. This is why germ cell neoplasms (testicular cancer as an e.g.), leukemias and lymphomas used to be very chemo-sensitive.

Fortunately, as time passed by, many other "resistant tumors" became sensitive to chemo due to increased knowledge about the multi-molecular mechanisms of tumor drug resistance, amazing pharmacologic developments (new targeted drugs and old ones used differently), properly-designed therapeutic schedules and clinical trials and new attempts to overcoming drug resistance from the perspective of the tumor microenvironment [3].

Through these novel approaches, sometimes we find that a small fraction of previously resistant patients responds unexpectedly well, presenting complete responses, better partial responses, or what is known in cancer as the most important end-point: prolonged overall survival. Initially, these kinds of patients were a matter of study at the National Cancer Institute (NCI) of the USA, but later many other research teams began to keep an eye on them.

Recently, when making an integrative analysis of an enormous profile of multi-platform genomics in exceptionally-responsive cancer patients, Wheeler et al. identified putative molecular mechanisms able to explain the survival phenotype in 23% of the cases [4]. Tumor biopsies from an unbiased cohort of 110 patients were studied to profile genetic and epigenetic alterations as well as the tumor microenvironment. Successful therapeutic outcomes are related to rare molecular features of the responding tumors that include synthetic lethal relationships. The mechanisms of action involved were assigned to four categories: DNA damage management, intracellular signaling, immune engagement and genetic biomarker characteristics of a favorable treatment response;

with many tumors falling into multiple categories. What is noteworthy is that some patients in this group present difficult-to-treat-entities, such as glioblastoma, pancreatic, biliary tract, ovarian and triple-negative breast cancers.

Nowadays, precision genomic and proteomic medicine are available and we have to analyze and review the clinical records of the patients involved with a critical eye. The take-home-message of this breviary is that seeking these exceptionally-responsive patients as well as analyzing their molecular profiles could help to find new mechanisms and/or biomarkers to be targeted not only in this kind of patient but also in those with a more classic treatment response. Isn't it awesome that ovarian cancer can respond to a drug currently used for renal cancer or a meningioma to topoisomerase II inhibitors? The answer is yes.

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